methylmalonic acidemia

Methylmalonic acidemia is an inherited disorder in which the body is unable to process certain proteins and fats (lipids) properly. The effects of methylmalonic acidemia, which usually appear in early infancy, vary from mild to life-threatening. Affected infants can experience vomiting, dehydration, weak muscle tone (hypotonia), developmental delay, excessive tiredness (lethargy), an enlarged liver (hepatomegaly), and failure to gain weight and grow at the expected rate (failure to thrive). Long-term complications can include feeding problems, intellectual disability, chronic kidney disease, and inflammation of the pancreas (pancreatitis). Without treatment, this disorder can lead to coma and death in some cases.

Frequency

This condition occurs in an estimated 1 in 50,000 to 100,000 people.

Genetic Changes

Mutations in the *MUT*, *MMAA*, *MMAB*, *MMADHC*, and *MCEE* genes cause methylmalonic acidemia. The long term effects of methylmalonic acidemia depend on which gene is mutated and the severity of the mutation.

About 60 percent of methylmalonic acidemia cases are caused by mutations in the *MUT* gene. This gene provides instructions for making an enzyme called methylmalonyl CoA mutase. This enzyme works with vitamin B12 (also called cobalamin) to break down several protein building blocks (amino acids), certain lipids, and cholesterol. Mutations in the *MUT* gene alter the enzyme's structure or reduce the amount of the enzyme, which prevents these molecules from being broken down properly. As a result, a substance called methylmalonyl CoA and other potentially toxic compounds can accumulate in the body's organs and tissues, causing the signs and symptoms of methylmalonic acidemia.

Mutations in the *MUT* gene that prevent the production of any functional enzyme result in a form of the condition designated mut^0. Mut^0 is the most severe form of methylmalonic acidemia and has the poorest outcome. Mutations that change the structure of methylmalonyl CoA mutase but do not eliminate its activity cause a form of the condition designated mut$^-$. The mut$^-$ form is typically less severe, with more variable symptoms than the mut^0 form.

Some cases of methylmalonic acidemia are caused by mutations in the *MMAA*, *MMAB*, or *MMADHC* gene. Proteins produced from the *MMAA*, *MMAB*, and *MMADHC* genes are needed for the proper function of methylmalonyl CoA mutase. Mutations that affect

proteins produced from these three genes can impair the activity of methylmalonyl CoA mutase, leading to methylmalonic acidemia.

A few other cases of methylmalonic acidemia are caused by mutations in the *MCEE* gene. This gene provides instructions for producing an enzyme called methylmalonyl CoA epimerase. Like methylmalonyl CoA mutase, this enzyme also plays a role in the breakdown of amino acids, certain lipids, and cholesterol. Disruption in the function of methylmalonyl CoA epimerase leads to a mild form of methylmalonic acidemia.

It is likely that mutations in other, unidentified genes also cause methylmalonic acidemia.

Inheritance Pattern

This condition is inherited in an autosomal recessive pattern, which means both copies of the *MUT*, *MMAA*, *MMAB*, *MMADHC*, or *MCEE* gene in each cell have mutations. Most often, the parents of an individual with an autosomal recessive condition are carriers of one copy of the mutated gene but do not show signs and symptoms of the condition.

Other Names for This Condition

- isolated methylmalonic acidemia
- methylmalonic aciduria
- MMA

Diagnosis & Management

Formal Diagnostic Criteria

- ACT Sheet: Elevated C3 acylcarnitine
  https://www.ncbi.nlm.nih.gov/books/NBK55827/bin/C3.pdf

Formal Treatment/Management Guidelines

- New England Consortium of Metabolic Programs: Acute Illness Protocol
  http://newenglandconsortium.org/for-professionals/acute-illness-protocols/organic-acid-disorders/methylmalonic-acidemia/

Genetic Testing

- Genetic Testing Registry: Methylmalonic acidemia
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C0268583/
- Genetic Testing Registry: Methylmalonic acidemia with homocystinuria cblD
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1848552/
- Genetic Testing Registry: Methylmalonic aciduria cblA type
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1855109/

- Genetic Testing Registry: Methylmalonic aciduria cblB type
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1855102/
- Genetic Testing Registry: Methylmalonic aciduria due to methylmalonyl-CoA mutase deficiency
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1855114/
- Genetic Testing Registry: Methylmalonyl-CoA epimerase deficiency
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1855100/

Other Diagnosis and Management Resources

- Baby's First Test: Methylmalonic Acidemia (Cobalamin Disorders)
  http://www.babysfirsttest.org/newborn-screening/conditions/methylmalonic-acidemia-cobalamin-disorders
- Baby's First Test: Methylmalonic Acidemia (Methymalonyl-CoA Mutase Deficiency)
  http://www.babysfirsttest.org/newborn-screening/conditions/methylmalonic-acidemia-methymalonyl-coa-mutase-deficiency
- GeneReview: Isolated Methylmalonic Acidemia
  https://www.ncbi.nlm.nih.gov/books/NBK1231
- MedlinePlus Encyclopedia: Methylmalonic acid
  https://medlineplus.gov/ency/article/003565.htm
- MedlinePlus Encyclopedia: Methylmalonic acidemia
  https://medlineplus.gov/ency/article/001162.htm
- New England Consortium of Metabolic Programs
  http://newenglandconsortium.org/for-families/other-metabolic-disorders/organic-acid-disorders/pa-and-mma/

General Information from MedlinePlus

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html
- Palliative Care
  https://medlineplus.gov/palliativecare.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

MedlinePlus

- Encyclopedia: Methylmalonic acid
  https://medlineplus.gov/ency/article/003565.htm
- Encyclopedia: Methylmalonic acidemia
  https://medlineplus.gov/ency/article/001162.htm
- Health Topic: Amino Acid Metabolism Disorders
  https://medlineplus.gov/aminoacidmetabolismdisorders.html
- Health Topic: Lipid Metabolism Disorders
  https://medlineplus.gov/lipidmetabolismdisorders.html
- Health Topic: Newborn Screening
  https://medlineplus.gov/newbornscreening.html

Genetic and Rare Diseases Information Center

- Methylmalonic acidemia
  https://rarediseases.info.nih.gov/diseases/7033/methylmalonic-acidemia

Educational Resources

- California Department of Health Services
  http://www.cdph.ca.gov/programs/nbs/Documents/NBS-ParentGuideMMA_June05.pdf
- CLIMB: Methylmalonic Acidemia Information Sheet
  http://www.climb.org.uk/IMD/Mike/MethylmalonicAcidaemia.pdf
- Disease InfoSearch: Methylmalonic acidemia
  http://www.diseaseinfosearch.org/Methylmalonic+acidemia/4713
- MalaCards: methylmalonic acidemia
  http://www.malacards.org/card/methylmalonic_acidemia
- My46 Trait Profile
  https://www.my46.org/trait-document?trait=Methylmalonic%20acidemia&type=profile
- New England Consortium of Metabolic Programs
  http://newenglandconsortium.org/for-families/other-metabolic-disorders/organic-acid-disorders/pa-and-mma/
- Orphanet: Vitamin B12-responsive methylmalonic acidemia
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=28
- Orphanet: Vitamin B12-responsive methylmalonic acidemia type cblA
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=79310

- Orphanet: Vitamin B12-responsive methylmalonic acidemia type cblB
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=79311
- Orphanet: Vitamin B12-unresponsive methylmalonic acidemia
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=27
- Orphanet: Vitamin B12-unresponsive methylmalonic acidemia type mut-
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=79312
- Screening, Technology, and Research in Genetics
  http://www.newbornscreening.info/Parents/organicaciddisorders/MMA.html
- Virginia Department of Health: Methylmalonic Aciduria (cblA and cblB)
  http://www.vdh.virginia.gov/content/uploads/sites/33/2016/11/Parent-Fact-Sheet_CblA-CblB_English.pdf
- Virginia Department of Health: Methylmalonic Aciduria (MUT)
  http://www.vdh.virginia.gov/content/uploads/sites/33/2016/11/Parent-Fact-Sheet_MUT_English.pdf

Patient Support and Advocacy Resources

- Children Living With Inherited Metabolic Diseases (CLIMB) (UK)
  http://www.climb.org.uk/
- National Organization for Rare Disorders (NORD)
  https://rarediseases.org/rare-diseases/acidemia-methylmalonic/
- Organic Acidemia Association
  http://www.oaanews.org/mma.html
- Resource list from the University of Kansas Medical Center
  http://www.kumc.edu/gec/support/metaboli.html

GeneReviews

- Isolated Methylmalonic Acidemia
  https://www.ncbi.nlm.nih.gov/books/NBK1231

ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22methylmalonic+acidemia%22

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28Amino+Acid+Metabolism,+Inborn+Errors%5BMAJR%5D%29+AND+%28%28methylmalonic+acidemia%5BTIAB%5D%29+OR+%28methylmalonic+aciduria%5BTIAB%5D%29+OR+%28mma%5BTIAB%5D%29+OR+%28methylmalonicacidemia%5BTIAB%5D%29+OR+%28methylmalonicaciduria%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D

OMIM

- METHYLMALONIC ACIDURIA AND HOMOCYSTINURIA, cblD TYPE
  http://omim.org/entry/277410
- METHYLMALONIC ACIDURIA DUE TO METHYLMALONYL-CoA MUTASE DEFICIENCY
  http://omim.org/entry/251000
- METHYLMALONIC ACIDURIA, cblA TYPE
  http://omim.org/entry/251100
- METHYLMALONIC ACIDURIA, cblB TYPE
  http://omim.org/entry/251110
- METHYLMALONYL-CoA EPIMERASE DEFICIENCY
  http://omim.org/entry/251120

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